

Nitroxide Radicals

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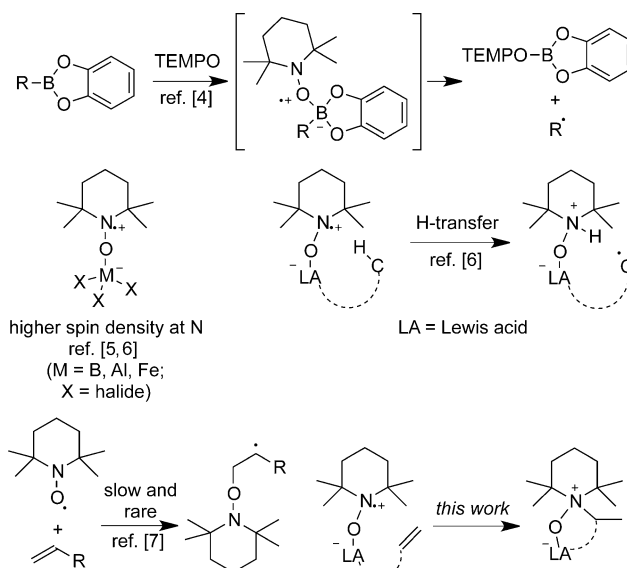
Selective N,O-Addition of the TEMPO Radical to Conjugated Boryldienes

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Abstract: $B(C_6F_5)_2$ -containing boryldienes **4** underwent the addition of two molar equivalents of TEMPO to give N,O-bonded four-membered heterocyclic products **7**. The reaction is a metal-free example of the generation of reactive nitrogen-centered TEMPO radical derivatives, in this case by the addition of TEMPO to the borane, followed by carbon–nitrogen bond formation and subsequent trapping of the resulting allyl radical by the second equivalent of TEMPO.

Nitroxide radicals, such as tetramethylpiperidine-1-oxyl (TEMPO, **1**) and its derivatives, are attracting increasing interest for use in organic synthesis, olefin-polymerization reactions (nitroxide-mediated polymerization, NMP), and materials science.^[1–3] Many reactions of TEMPO have been reported, including reactions involving hydrogen-atom abstraction, the trapping of reactive radicals, and oxidation/reduction sequences.^[1–3] Mostly, TEMPO shows reactivity at the O atom, where the highest spin density is found. However, upon the complexation of TEMPO with a Lewis acid (LA), the spin distribution and accordingly the reactivity profile of TEMPO might change.

Along these lines, there have been some reports on the reactivity of LA-complexed TEMPO. Renaud and co-workers found that alkyl radicals can be generated by the treatment of TEMPO with alkyl catecholboranes (Scheme 1; similar to ethyl-radical generation from triethylborane and dioxygen).^[4] It is assumed that TEMPO first undergoes Lewis acid/base adduct formation, and that this intermediate then undergoes β -fragmentation to the corresponding alkyl radical along with TEMPO–catecholborate. This reaction can be understood by considering the resonance structure of the LA/LB adduct, in which the spin is located at the O atom (Scheme 1). It is known that the complexation of TEMPO with boron-, aluminum-, or iron-based Lewis acids leads to an increase in the spin density at the N atom,^[5] and this increase in spin density should provide aminyl radical–cation character to the nitroxide. Indeed, it has been shown that intra- and intermolecular H-abstraction by the N atom in such LA/LB adducts is feasible.^[6] However, reactions other than simple H-abstraction by such complexed aminyl radical cations are uncommon. We assumed that, in analogy with the



Scheme 1. Alteration of the reactivity of TEMPO through adduct formation with Lewis acids.

well-established cyclization of aminyl radicals,^[8] appropriately alkene substituted TEMPO–LA adducts might undergo C–N bond-forming radical cyclization reactions. Notably, for steric reasons, TEMPO shows very low reactivity towards alkenes in the absence of a LA, and if it does undergo addition to an alkene, the reaction occurs at the O atom of the nitroxide (Scheme 1).^[7]

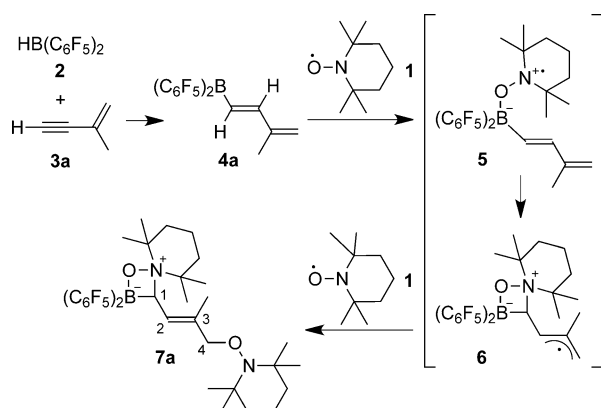
Herein we disclose that boryl-substituted alkenes can react very selectively with TEMPO through LA/LB adduct formation and subsequent 4-*exo* cyclization of the resulting aminyl radical. The unusual process involves bond formation to both the TEMPO oxygen and nitrogen atom.

We generated the dienyl borane **4a** by hydroboration of the conjugated enyne **3a**^[9] with the Piers borane, $HB(C_6F_5)_2$ (**2**).^[10] The boryldiene **4a** was then exposed to two molar equivalents of TEMPO (**1**) in benzene solution. The reaction proceeded quickly to completion (20 min, room temperature). Workup eventually gave the product **7a** as a solid in 84 % yield (see Scheme 2). Single crystals of **7a** suitable for X-ray crystal-structure analysis were obtained at -30°C from a solution in toluene covered with a layer of heptane. The crystal structure showed that two TEMPO radicals had added to the boryldiene starting material (Figure 1).

The X-ray crystal-structure of **7a** showed that one TEMPO molecule had added to the boron atom of the strongly electrophilic borane to form a new B–O bond, as

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Scheme 2. Suggested mechanism for the formation of compound **7a**.

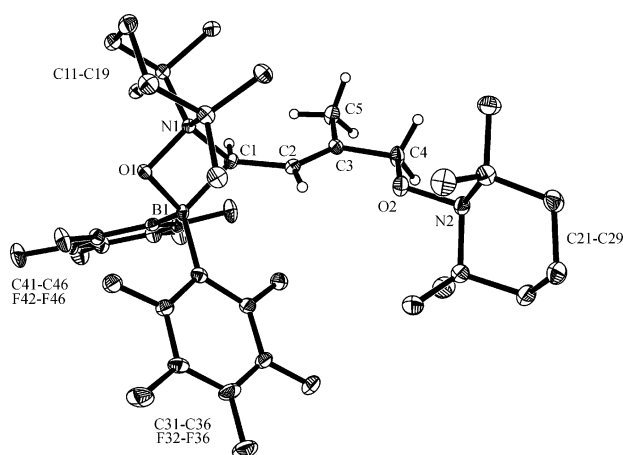


Figure 1. Molecular structure of **7a** (thermal ellipsoids are shown with 15 % probability; hydrogen atoms of the tetramethylpiperidine ring are omitted for clarity). Selected bond lengths [Å] and angles [°]: B1–O1 1.535(6), B1–C1 1.649(8), N1–O1 1.441(5), N1–C1 1.589(6), N2–O2 1.445(5), O2–C4 1.430(6), C1–C2 1.471(7), C2–C3 1.337(7), C3–C4 1.495(7); O1–B1–C1 87.3(4), B1–C1–N1 85.0(3), B1–O1–N1 94.5(3), O1–N1–C1 93.0(3), C4–O2–N2 110.3(4), C1–N1–O1–B1 3.5(4), C1–C2–C3–C4 –178.9(5), B1–C1–C2–C3 136.5(6), $\Sigma \text{N2}^{\text{CCO}}$ 330.9.[13]

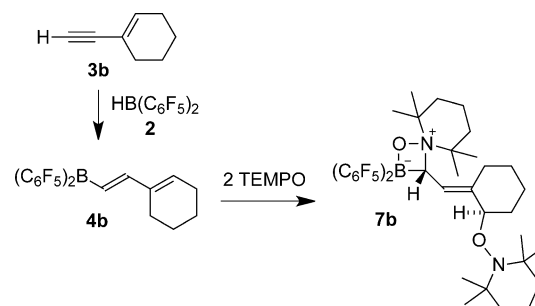
expected. According to our design principle, the nitrogen atom of that TEMPO unit had cyclized onto the α carbon atom (C1) of the adjacent dienyl moiety to form a four-membered B,O,N,C heterocycle. The ring was almost planar (sum of the internal angles: 359.8° , $\theta(\text{B1-C1-C2-C3}) = 136.5(6)^\circ$). The second TEMPO equivalent had added to the terminal carbon atom of the C_4 chain to form a new oxygen–carbon bond, as is often seen in trapping reactions of TEMPO radicals.[1–3] Nitroxide trapping occurred with high regio- and diastereoselectivity to afford the product **7a** with an *E*-configured $\text{C2}=\text{C3}$ double bond.

The diamagnetic addition product **7a** showed an ^{11}B NMR signal at $\delta = 2.4$ ppm. It featured the ^{19}F NMR resonances of a pair of diastereotopic C_6F_5 substituents at boron that show hindered rotation around the B–C vectors at 299 K. The ^1H NMR spectrum showed an olefinic $=\text{C2H}$ signal at $\delta = 6.35$ ppm with the resonance of the adjacent *tert*-C1H atom at $\delta = 5.88$ ppm [^{13}C : $\delta = 138.1$ (C3), 120.4 (C2), 71.8 ppm (C1)]

(atom numbering scheme as depicted in Scheme 2 and Figure 1). There were a total of nine separate CH_3^1H NMR resonances owing to the chirality features of compound **7a**: four for each TEMPO residue and one for the methyl group at C3 (see the Supporting Information for further details).

We assume that the reaction is initiated by the addition of TEMPO to the electrophilic boron atom of the strongly Lewis acidic $\text{B}(\text{C}_6\text{F}_5)_2$ substituent; the reaction profits from the high oxophilicity of the boron atom. This step probably results in the formation of the intermediate zwitterionic borate anion/amine radical cation **5** (see Scheme 2). The coordination to boron leads to a higher spin density at the nitrogen atom in that TEMPO unit.[5,6,11] In contrast to TEMPO–[M] adducts, which often undergo H-atom abstraction reactions to give the diamagnetic [N]–H products,[6,11] the nitrogen-radical site in **5** adds to the adjacent internal dienyl π -system in a 4-*exo* cyclization to give the four-membered heterocycle by N–C bond formation with the generation of an attached methallyl radical. This allyl radical is then rapidly trapped regioselectively by an additional TEMPO equivalent to eventually yield the observed product **7a**. It is likely that TEMPO trapping occurred at the terminal position for steric reasons.

This reaction is not a singular case of this remarkable reactivity pattern. The more bulky dienyl borane **4b** (prepared by the addition of $\text{HB}(\text{C}_6\text{F}_5)_2$ to the alkynyl moiety of the corresponding enyne **3b**) also reacted rapidly by double TEMPO addition (10 min, room temperature, benzene) to give the product **7b** as a crystalline material in 85 % yield (see Scheme 3). X-ray crystal-structure analysis confirmed prod-



Scheme 3. Reaction of **4b** with TEMPO to provide compound *rac*-**7b**.

uct formation through O,N-TEMPO addition to the boryl-diene terminus and addition of the second TEMPO molecule to the diene carbon atom C4. In this case, two stereogenic centers were formed in the course of the addition process. The reaction occurred highly stereoselectively. We found both diastereoisomers in the crystal [*rac*-1*R*,4*S* (86 %; Figure 2) and *rac*-1*S*,4*S* (14 %)] and observed the typical NMR resonances of a major diastereoisomer (96 %) in solution (CD_2Cl_2 , ^{11}B : $\delta = 2.4$ ppm; see the Supporting Information for further details).

We confirmed the generation of a carbon-centered radical intermediate by treatment of the cyclopropyl-substituted alkenyl borane **4c** with two equivalents of TEMPO (Scheme 4). The reaction was rather slow at room temper-

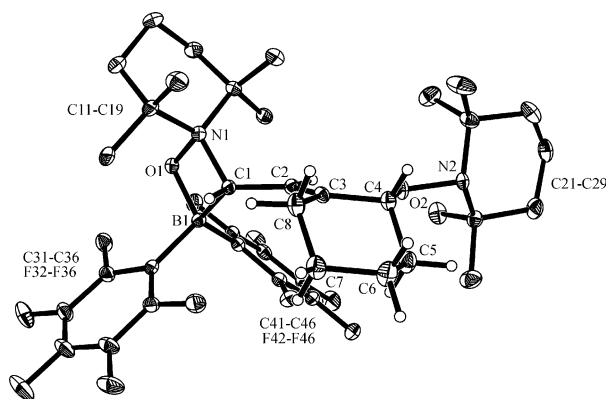


Figure 2. Molecular structure of *rac*-(1*S*,4*R*)-**7b** (thermal ellipsoids are shown with 15% probability; hydrogen atoms of the tetramethylpiperidine ring are omitted for clarity). Selected bond lengths [Å] and angles [°]: O1–N1 1.449(4), O1–B1 1.532(4), C1–C2 1.487(5), C1–N1 1.577(4), C1–B1 1.635(5), O2–C4 1.433(4), O2–N2 1.459(3); B1–C1–C2–C3 –134.4(5), Σ (internal angles B1C1N1O1) 359.8, Σ N2^{CCO} 327.7.^[13]

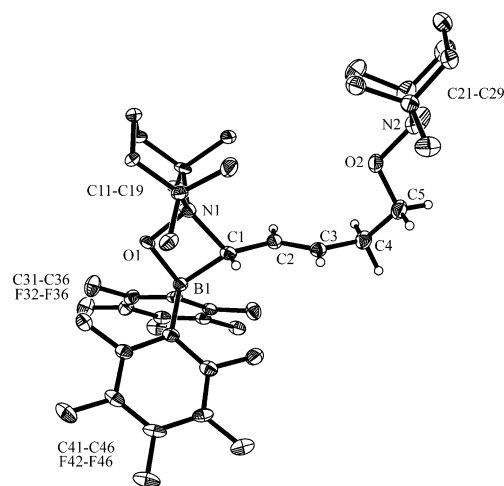
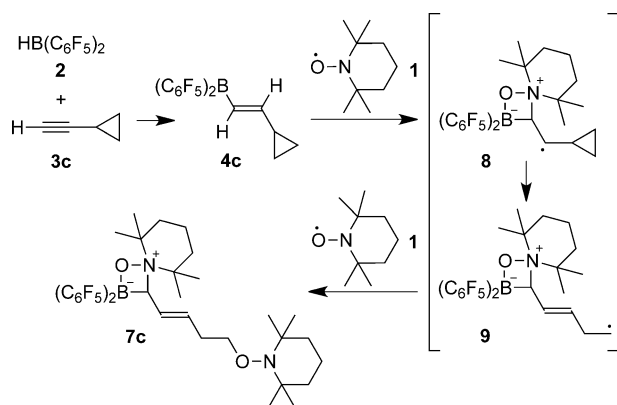


Figure 3. Molecular structure of **7c** (thermal ellipsoids are shown with 30% probability; hydrogen atoms of the tetramethylpiperidine ring are omitted for clarity).^[13]



Scheme 4. Suggested reaction pathway for the formation of compound **7c**.

ature, and we isolated the product **7c** in approximately 30% yield after 5 days. Compound **7c** was characterized by spectroscopy and by X-ray diffraction (Figure 3; see the Supporting Information for further details). We assume that the radical intermediate **8** generated by ring closure undergoes the typical ring-opening rearrangement of cyclopropylmethyl radicals to eventually give the product **7c** after trapping with the second equivalent of TEMPO (Scheme 4).

Finally, we tested adducts **7a** and **7b** as initiators/regulators in the nitroxide-mediated radical polymerization (NMP) of styrene (see the Supporting Information for details).^[2a,b] With both alkoxyamines, polymerization did not occur below 115°C. In the case of **7a**, moderate control of styrene polymerization was observed at 125°C with PDI values at the theoretical limit for controlled radical polymerizations (1.42–1.56). For example, polymerization with **7a** (0.5 mol %) for 5 h provided, after precipitation, polystyrene with a number-average molecular weight (M_n) of 6400 g mol^{−1} and a polydispersity index (PDI) of 1.48 (41% yield). As compared to **7a**, alkoxyamine **7b** was a more efficient

initiator/regulator. The best results were observed at 130°C, with the formation of polystyrene with PDI values ranging from 1.31 to 1.39 (for example, with 0.5 mol % of **7b**, 5 h: 21% yield, M_n = 5200 g mol^{−1}, PDI = 1.32; for a full set of data on the polymerization studies, see the Supporting Information). Controlled polymerization was rather slow at 130°C, and a further increase in the reaction temperature to 135°C led to an increased PDI value. Hence, the average molecular weight of polystyrene obtained with **7a** and also with **7b** could be adjusted on the basis of the amount of initiator used (0.1–2.5 mol %). However, polymerization control was moderate and conversion generally low, thus indicating loss of livingness at longer reaction times.

In summary, our study has shown that the presence of a strongly Lewis acidic boryl group has a pronounced effect on the addition reaction of the TEMPO radical to an adjacent unsaturated moiety. It seems that we have found a similar influence of the boron atom on the TEMPO radical to that described for some transition-metal/TEMPO adducts, namely, a transformation from a predominantly oxygen centered radical to nitrogen-radical properties. In our case, this transformation resulted in the formation of a four-membered heterocyclic substructure by 4-exo radical cyclization followed by TEMPO trapping to give the final diamagnetic products **7**. It remains to be seen whether this metal-free “radical-site Umpolung” can be extended to other unsaturated borane derivatives and other TEMPO derivatives^[1] or analogues^[12] for new applications in radical-based chemistry.

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- [13] CCDC 1427622 (**7a**), 1427623 (**7b**), and 1438006 (**7c**) contain the supplementary crystallography data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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